

PACIFEN



1. Product Name

PACIFEN, 10 mg or 25 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 10 mg or 25 mg of baclofen

PACIFEN tablets contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

PACIFEN 10 mg tablets are white, round, flat bevelled edged marked 'BN' | '10' on one side and 'G' on the other. Each tablet contains 10 mg of baclofen and has a diameter of 7 mm.

PACIFEN 25 mg tablets are white, round, flat bevelled edged marked 'BN' | '25' on one side and 'G' on the other. Each tablet contains 25 mg of baclofen and has a diameter of 8 mm.

4. Clinical Particulars

4.1 Therapeutic indications

Spasticity of the skeletal muscles in multiple sclerosis. Spastic conditions occurring in spinal-cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

4.2 Dose and method of administration

Treatment should always be initiated with small, gradually increasing doses of PACIFEN. The optimum daily dosage should be individually adapted to the patient's requirements in such a way that clonus, flexor and extensor spasms, and spasticity are reduced, but that adverse effects are as far as possible avoided.

In order to prevent excessive weakness and falling, PACIFEN should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion or whenever spasticity is used to maintain function. It may be important to maintain some degree of muscle tone and allow

occasional spasms to help support circulatory function. PACIFEN should be taken during meals with a little liquid.

The daily dosage should be given in divided doses, preferably 3 in adults and 4 in children.

Dose

Adults

Treatment should as a rule be started with a dosage of 5 mg, 3 times daily, which, for the purpose of cautious dose titration, should subsequently be increased at 3-day intervals by 5 mg, 3 times daily until the requisite daily dosage has been attained. In certain patients reacting sensitively to medicines, it may be advisable to begin with a lower daily dosage (5 mg or 10 mg) and to raise this dosage more gradually. The optimum dosage generally ranges from 30 mg to 80 mg daily. Daily doses of 100 to 120 mg may be given to carefully supervised patients in hospital.

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision whether to continue with PACIFEN should be taken.

Special populations

Children

Treatment should usually be started with a very low dose, e.g. 0.3 mg/kg a day, in divided doses. The dosage should be raised cautiously, at about 1 to 2 week intervals, until it becomes sufficient for the child's individual requirements. The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. In children over 10 years of age, however, a maximum daily dosage of 2.5 mg/kg body weight may be given.

Impaired renal function

In patients with impaired renal function baclofen should be given with caution and in lower doses. In patients undergoing chronic haemodialysis, baclofen concentrations in plasma are elevated and therefore a particularly low dosage of PACIFEN should be selected, i.e. approx. 5 mg daily.

Elderly

Since unwanted effects are more likely to occur in elderly patients or in patients with spastic states of cerebral origin, it is recommended that a very cautious dosage schedule be adopted in such cases and that the patient be kept under appropriate surveillance.

4.3 Contraindications

- Known hypersensitivity to baclofen or any of the components of the formulation listed in section 6.1.
- Peptic ulceration.

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders

Patients suffering not only from spasticity but also from psychotic disorders, schizophrenia, depressive or manic disorders, confusional states should be treated cautiously with baclofen and kept under careful surveillance, because exacerbations of these conditions may occur.

Epilepsy or other potential convulsive conditions

Caution is needed in patients with epilepsy or other convulsive conditions, cortical or subcortical brain damage or significant EEG abnormalities, since ingestion of baclofen may cause deterioration

of seizure control and EEG changes, and may precipitate convulsions. In patients with epilepsy and muscle spasticity, baclofen can be used under appropriate supervision, provided adequate anticonvulsive therapy is continued.

Lowering of the convulsion threshold may occur and seizures have been reported occasionally after cessation of baclofen or with overdosage.

Other concomitant conditions

Baclofen should be used with caution in patients with:

- cerebrovascular diseases/accidents or respiratory or hepatic insufficiency
- porphyria
- a history of alcoholism
- diabetes mellitus (baclofen may increase blood glucose concentrations)
- hypertension (see section 4.5).

Since unwanted effects are more likely to occur, a cautious dosage schedule should be adopted in elderly and patients with spasticity. Baclofen is not recommended in Parkinson's disease or spasticity arising from strokes, cerebral palsy or rheumatoid disorders.

Changes in muscle tone

Baclofen should be used with caution in patients who use spasticity to maintain an upright posture and balance in moving. If an undesirable degree of muscular hypotonia occurs, making it more difficult for patients to walk or fend for themselves, this can usually be relieved by adjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

During treatment with baclofen, neurogenic disturbances affecting emptying of the bladder may improve, whereas in patients with pre-existing sphincter hypertonia, acute retention of urine may occur. The drug should, therefore, be used with caution in such cases.

Hepatic impairment

Because baclofen is partially metabolised in the liver, patients with impaired liver function should be periodically monitored with laboratory tests.

Renal impairment

Since baclofen is largely eliminated by the kidneys, a dosage reduction is advised to avoid drug accumulation.. Baclofen should be used with caution in patients with renal impairment and should be administered to patients with end-stage renal failure only if the expected benefit outweighs the potential risk. Neurological signs and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, somnolence, hallucination) have been observed in patients with renal impairment taking baclofen at doses at and above 5 mg daily. Patients with renal impairment should be closely monitored for prompt diagnosis of early signs and symptoms of toxicity (see section 4.9).

Particular caution is required when combining baclofen to drugs or medicinal products that can significantly impact renal function. Renal function shall be closely monitored and baclofen daily dosage adjusted accordingly to prevent baclofen toxicity.

Besides discontinuing treatment, unscheduled haemodialysis might be considered as a treatment alternative in patients with severe baclofen toxicity. Haemodialysis effectively removes baclofen from the body, alleviates clinical symptoms of overdose and shortens the recovery time in these patients.

Abrupt discontinuation

Anxiety and confusional states, delirium, hallucinations, psychotic disorders, mania, or paranoia, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia and - as a rebound phenomenon- temporary aggravation of spasticity have been reported upon the abrupt withdrawal of baclofen, especially after long-term medication.

Drug withdrawal reactions including postnatal convulsions have been reported after intrauterine exposure to oral baclofen (see section 4.6).

Except in overdose-related emergencies or where serious adverse effects have occurred, treatment should therefore always be gradually withdrawn by successive dosage reduction over a period of approximately 1 to 2 weeks.

If withdrawal symptoms occur, restarting baclofen therapy and withdrawing over a longer period may help to resolve withdrawal problems.

Switching from oral to intrathecal baclofen and vice versa

An attempt should be made to discontinue concomitant antispastic medication to avoid possible overdose or adverse drug interactions. This should preferably be done before switching from oral to intrathecal baclofen or vice versa and requires careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics during chronic therapy with baclofen should be avoided.

Posture and balance

Baclofen should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see section 4.2).

Monitoring advice

Since in rare instances elevated AST, alkaline phosphatase or glucose levels in the serum have been recorded, appropriate laboratory tests should be performed periodically in patients with liver diseases or diabetes mellitus, in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Careful monitoring of respiratory and cardiovascular function is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

4.5 Interaction with other medicines and other forms of interaction

Levodopa/dopa decarboxylase (DDC) inhibitor (carbidopa)

In patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combination with DDC inhibitor, carbidopa), there have been reports of mental confusion, hallucinations, headaches, nausea and agitation. Worsening of the symptoms of Parkinsonism has also been reported. Hence, caution should be exercised during concomitant administration of baclofen and levodopa/carbidopa.

Drugs causing central nervous system (CNS) depression

Increased sedation may occur when baclofen is taken concomitantly with other agents causing CNS depression including other muscle relaxants (such as tizanidine), synthetic opiates or with alcohol (see section 4.4) The risk of respiratory depression is also increased. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

Antidepressants

During concurrent treatment with tricyclic antidepressants, the effect of baclofen may be potentiated, resulting in pronounced muscular hypotonia.

Lithium

Concurrent use of baclofen and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when baclofen is used concomitantly with lithium.

Antihypertensives

Since concomitant treatment with baclofen and antihypertensive agents is likely to increase the risk of hypotension, the dosage of antihypertensive medication should be adjusted accordingly.

Agents reducing renal function

Drugs or medical products that can significantly impact renal function may reduce baclofen excretion leading to toxic effects (see section 4.4).

Others

The concurrent use of baclofen with monoamine oxidase inhibitors (MAOIs) may result in increased CNS-depressant and hypotensive effects. Caution is recommended and dosage of one or both agents may require reduction.

Since baclofen may increase blood glucose concentrations, dosage adjustments of insulin and/or oral hypoglycaemic agents may be necessary during and after concurrent therapy.

Studies in rats indicate that the agonistic effects of baclofen on gastric acid secretion are potentiated by diazepam.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3

There are no adequate and well-controlled studies in pregnant women. Animal data showed that baclofen crosses the placental barrier. Therefore, baclofen should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus.

Drug withdrawal reactions including postnatal convulsions in neonates following intra-uterine exposure to oral baclofen, have been reported. In one suspected case of postnatal baclofen withdrawal, the convulsions were refractory to various anticonvulsants, but responsive to the administration of baclofen to the affected neonate (see section 4.4).

Use in lactation

Studies in lactating women are limited to one (1) patient. In this particular case, available evidence suggests that baclofen is found in quantities so small that undesirable effects in the infant would have been unlikely.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Baclofen may be associated with adverse effects such as dizziness, sedation, somnolence and visual disturbance (see section 4.8) which may impair the patient's reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines.

The patient's ability to react may be adversely affected by sedation and decreased alertness caused by baclofen; patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Adverse effects mainly occur at the start of treatment (e.g. sedation, somnolence), if the dosage is increased too quickly, if large doses are used, or if the patient is elderly. They are often transitory and can be attenuated or eliminated by reducing the dosage. They may necessitate withdrawal of the medication. In patients with a history of psychiatric illness, cortical or organic brain disorders, or with cerebrovascular disorders (such as stroke), as well as in elderly patients, adverse reactions may be more serious.

It is often difficult to distinguish whether some of these are drug effects or manifestations of the diseases under treatment. Psychiatric manifestations can occur in acute or chronic toxicity due to baclofen.

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients (see section 4.4).

Certain patients have shown increased muscle spasticity as a paradoxical reaction to the medication.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Nervous system disorders

Very common: sedation, somnolence.

Common: respiratory depression, fatigue, confusional state, dizziness, personality changes, vertigo, headache, insomnia, euphoric mood, depression, muscular weakness, ataxia, tremor, hallucination, nightmare, myalgia, nystagmus, dry mouth, tinnitus.

Rare: paraesthesia, dysarthria, dysgeusia, syncope, dyskinesia, coma, taste disturbances.

Very rare: hypothermia.

Eye disorders

Common: accommodation disorders, visual impairment.

Cardiac disorders

Common: cardiac output decreased.

Rare: arrhythmias, palpitations, chest pain.

Not known: bradycardia.

Vascular disorders

Common: hypotension.

Rare: dyspnoea, ankle oedema.

Gastrointestinal disorders

Very common: nausea (particularly at the start of treatment).

Common: gastrointestinal disorder, retching, vomiting, constipation, diarrhoea. Rare: colicky abdominal pain, anorexia.

Hepatobiliary disorders

Rare: hepatic function abnormal.

Skin and subcutaneous tissue disorders

Common: hyperhidrosis, rash, pruritus.

Not known: urticaria.

Renal and urinary disorders

Common: pollakiuria, enuresis, dysuria.

Rare: urinary retention, nocturia, haematuria.

Reproductive system and breast disorders

Rare: erectile dysfunction, inability to ejaculate.

General disorders and administration site conditions

Very rare: hypothermia.

Not known: drug withdrawal syndrome*.

Investigations

Not known: blood glucose increase.

Miscellaneous

Rare: nasal congestion, weight gain.

* Drug withdrawal syndrome including postnatal convulsions has also been reported after intra-uterine exposure to oral baclofen.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Signs and symptoms

Prominent features are signs of central nervous depression: somnolence, impairment of consciousness, respiratory depression due to absent respiratory movement, coma.

Also liable to occur are: confusion, hallucinations, agitation, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia or cardiac arrhythmias; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes, sleep apnoea, rhabdomyolysis.

A deterioration in the condition may occur if various substances or drugs acting on the central nervous system (e.g. alcohol, diazepam, tricyclic antidepressants) have been taken at the same time.

Adult patients have ingested up to 1,125 mg of baclofen and survived. Ingestion of 1,250 to 2,500 mg by one patient was fatal. Serious poisoning has occurred with doses of 150 and 300 mg in adults.

Treatment

No specific antidote is known.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disturbances, and respiratory or cardiovascular depression.

Symptomatic treatment should include the following:

- elimination of the drug from the gastrointestinal tract e.g. administration of activated charcoal; if necessary, saline laxatives
- since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic
- measures in support of cardiovascular functions
- in the case of respiratory muscle weakness, administration of artificial respiration
- in the event of convulsions, diazepam should be administered cautiously intravenously, paying attention to increased muscle relaxation, and possible respiratory insufficiency, if the patient is not already being artificially ventilated
- haemodialysis (sometimes unscheduled) may be useful in severe poisoning associated with renal failure (see section 4.4).

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: muscle relaxant, centrally acting agents, ATC code: M03BX01

Mechanism of action

Baclofen is an effective antispastic agent with a spinal site of action. Its mechanism of action and pharmacological properties are different from those of other antispastic agents. Baclofen also has central sites of action given the adverse event profile and general CNS depressant properties.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by various actions, including stimulation of GABA_β-receptors. This stimulation in turn inhibits the release of excitatory amino acids (glutamate and aspartate). Neuromuscular transmission is not affected by baclofen.

Baclofen exerts an antinociceptive effect. The clinical significance of this awaits clarification. In neurological diseases associated with spasm of the skeletal muscles, the clinical effects of baclofen take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism, and clonus. Baclofen, where indicated, improves the patient's mobility, making for greater independence, and facilitating passive and active physiotherapy. Baclofen stimulates gastric acid secretion.

5.2 Pharmacokinetic properties

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract. Maximum concentrations of unchanged drug are achieved in plasma in 2 to 4 hours after an oral dose. The bioavailability of oral baclofen is 70-80%.

Following oral administration of a single dose of 40 mg baclofen, a peak serum concentration between 500 to 600 nanogram/mL was reached. The serum concentration remains above 200 nanogram/mL for 8 hours. The onset of action is highly variable and may range from hours to weeks.

Distribution

The distribution volume of baclofen amounts to 0.7 L/kg. In cerebrospinal fluid, the active substance attains concentrations approximately 8.5 times lower than in the plasma.

Baclofen is bound to plasma proteins to the extent of about 30%.

Metabolism

About 15% of the baclofen dose is metabolised in the liver. Deamination yields the main metabolite, β-(chlorophenyl)-γ-hydroxybutyric acid, which is pharmacologically inactive.

Elimination

Approximately 70% of baclofen is eliminated in the urine in the unchanged form. The plasma elimination half-life of baclofen averages 3 to 4 hours. Within 72 hours, approximately 75% of the dose is excreted via the kidneys, approximately 5% of this quantity being in the form of metabolites. The remainder of the dose, including 5% as metabolites, is excreted in the faeces.

5.3 Preclinical safety data

Animal data

In two teratogenic studies in pregnant rats, baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses at a dose of 20 mg/kg/day, which is maternotoxic. The relevance of this finding to humans is unknown. At the same dose there was also an increased incidence of incomplete sternebral ossification in the fetuses.

In mice, no teratogenic effects were observed at a dose of 81.5 mg/kg/day given via the diet or up to 40 mg/kg/day given by gavage. At 40 mg/kg/day by gavage, a delay in fetal growth was associated with maternal anorexia. The lack of maternotoxicity seen in the dietary study suggests that the dose used was inadequate.

In pregnant rabbits, oral doses up to 10 mg/kg/day were manifested as a sedative effect. Skeletal examination of fetuses revealed a marked increase in the absence of ossification of the phalangeal nuclei of fore-limbs and hind-limbs.

Carcinogenicity

A two year carcinogenicity study in rats found no evidence that baclofen had carcinogenic potential at oral doses up to 100 mg/kg/day. An apparently dose related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the highest two doses (50 and 100 mg/kg/day) was observed in female rats. The clinical relevance of these findings is not known.

Ovarian cysts have been found by palpation in about 5% of the multiple sclerosis patients who were treated with oral baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are known to occur spontaneously in a proportion of the normal female population.

Genotoxicity

Baclofen did not induce mutations in bacterial or mammalian cells in vitro, lacked DNA damaging activity in the sister chromatid exchange assay, and had no clastogenic activity in the nuclear anomaly test.

6. Pharmaceutical Particulars

6.1 *List of excipients*

PACIFEN tablets also contain the following inactive ingredients:

- lactose
- cellulose – microcrystalline
- calcium hydrogen phosphate anhydrous
- sodium starch glycollate
- silica – colloidal anhydrous
- magnesium stearate

PACIFEN tablets are gluten free.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

3 years.

6.4 *Special precautions for storage*

Store at or below 25°C.

6.5 *Nature and contents of container*

PACIFEN 10 mg tablets: HDPE bottles with PP cap of 50's, 100's and 250's.

PACIFEN 25 mg tablets: HDPE bottles with PP cap of 100's.

Not all strengths or pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

18 September 1986

10. Date of Revision of the Text

20 July 2018

Section	Summary of changes
-	Revised to SmPC format
4.4	Sections added: switching from oral to IV routes. Sections updated: Psychiatric and nervous symptoms disorders, other conditions, hepatic impairment, renal impairment, abrupt discontinuation. Sections removed: patients with spastic sates of cerebral origin, paediatric use, use in elderly.
4.5	Addition of interaction: levodopa/dopa decarboxylase (DDC) inhibitor (carbidopa)
4.6	Pregnancy section updated.
4.8	Removal of advice re nausea & muscular hypotonia.
4.9	Updated signs and symptoms of overdose
5.1	Updated mechanism of action.
5.2	Removal of special populations pharmacokinetics.
5.3	Updated animal data.